IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S, Plaintiff v. GENENCOR INTERNATIONAL, INC., and ENZYME DEVELOPMENT CORPORATION Defendants	C.A. No. 05-160-KAJ

PLAINTIFF NOVOZYMES' POST-TRIAL REPLY BRIEF

Josy W. Ingersoll (No. 1088)
Rolin P. Bissell (No. 4478)
Andrew A. Lundgren (No. 4429)
YOUNG CONAWAY STARGATT & TAYLOR, LLP
1000 West Street, 17th Floor
Wilmington, Delaware 19801
(302) 571-6600
alundgren@ycst.com

Attorneys for Plaintiff Novozymes A/S

OF COUNSEL
Joseph R. Robinson (*Pro Hac Vice*)
Robert C. Sullivan, Jr. (*Pro Hac Vice*)
Samuel S. Woodley (*Pro Hac Vice*)
DARBY & DARBY PC
805 Third Avenue
New York, New York 10022-7513
(212) 527-7700

Dated: May 12, 2006

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I. INTRODUCTION

Claims 1, 3 and 5 of the '031 patent are literally infringed, despite Genencor's cryptic reinterpretation of certain claim terms. **NPTB at 22-26; NPTO at 39-40.**[1] The patent is not invalid or unenforceable because of Machius '95 or the Borchert Declaration. **NPTB at 26-40; NPTO at 8-27.** Stripped of attack-mode rhetoric, Genencor's Opposition is toothless and unfounded.

According to Genencor, "Machius '95 adds to the motivation and confidence" provided by Suzuki. **GPTO at 7.** This comes from the "loop" idea, described by Dr. Machius as a "minor aspect, one specific aspect, namely the loop shortening that Suzuki [*sic*] observed" for BAN. **GPTO at 3** (quoting **A6572**). This did not translate into a forecast of reasonable success for BSG, nor to the strikingly superior BSG variants of the '031 patent. **NPTB at 31-32; NPTO at 11, 25.** Hindsight from "loop shortening" in low-stability BAN was not foresight that high-stability BSG variants would be super-stable. A shorter loop could stabilize or destabilize. **NPF ¶231; A5720:20-5721:3.** Success was no better than 50/50. **A6107:2-13.** The magnitude, even the fact of a stability increase was unpredictable. **NPF ¶225; A5721:21-5722:4.** This was especially true in a low-calcium context, important for the invention. **A6534:7-14; A6535:17-19.** Machius was cumulative, incomplete, and equivocal. **A5641:2-6; A5660:12-18.** Suzuki was the closest prior art; there was no need or thought to cite Machius.[2] There was no calculated omission done with manifest intent to deceive. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1353, 1367 (Fed. Cir. 2003) (no inference of deceit akin to fraud "where the reasons given for the withholding are plausible.").

The claimed BSG variants are much more improved than a protein engineer could reasonably expect in 1995. They crossed into a rare class of high-performance alpha-amylases, not prophesied in the prior art. **NPTB at 28-30; NPTO at 22-24.** Genencor had no contrary experi-

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[1] Genencor's Findings are cited as **GPF, ¶X**; its Conclusions are **GCL, ¶X**; its Post Trial Brief is **GPTB at X**; its Opposition is **GPTO at X.** Novozymes' Findings & Conclusions are **NPF, ¶X**; its Post-Trial Brief is **NPTB at X**; its Opposition is "**NPTO at X.**" Emphases in quotations are added unless otherwise stated.

[2] *See* **A4645:21-5646:4; A5602:20-24; A5631:15-5632:4, A5633:12-5637:2; A5637:25-A5638:18; A5660: 17-18; A5662:11-18; A5671:4-A5672:22-5677:1-4; TE-110, A8169-71.**

ments and used "arbitrary" phantom data to argue for only a modest and routine improvement. **NPTO at 24; NPF ¶185, 356.** Its deconstruction of the Borchert Declaration revealed diligent scientific inquiry and principled advocacy, not inequitable conduct. **NPTB at 38-39; NPTO at 23.**

Genencor accuses Novozymes of misusing the Borchert data and omitting Machius to "carry out its option plan and obtain a patent" **GPTO at 15**. Pursuing a patent to arm against "me-too" competition was not inequitable, nor a special case of laches. **NPTO at 8-9; NPF ¶409-412**.

A straightforward and proper reading of the claims and a level comparison with Spezyme Ethyl shows naked infringement. **NPTB at 22-26**. Genencor cannot exempt itself by grafting extraneous limitations onto the claims, so that it can deny them in its infringing product.

II. ARGUMENT

Genencor projects wrong-doing onto others to save itself, but its fiction is not fact. What really happened is much more pedestrian: literal infringement of a valid and enforceable patent.

A. The '031 Patent Is Valid Over Machius

Genencor argues that Novozymes put Dr. Machius on a pedestal but knocks him down here. **GPTO at 1-2**. This is thoroughly misplaced because it makes no link between the reference and the claimed 179,180 BSG variants. Obviousness rests on critical factual underpinnings: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention, (3) the level of skill in the art, and (4) the objective indicia of non-obviousness. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1566-67 (Fed. Cir. 1987); *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Speaking with Dr. Machius or citing his work elsewhere does not address these points. Academic discourse is not an endorsement. Dr. Machius gave a talk and had dinner with Dr. Borchert. ***Id.*** This is extraneous to Machius '95 and its import on 179,180 BSG variants, if any.

Dr. Borchert cited Machius '95 in a slide-show for its crystal structure of *B. licheniformis* (BLA) alpha-amylase. **TE-664, A9046-48**. The slide-show concerned a search for low-temperature (20-55°C) and high-pH (alkaline) alpha-amylases (**A9045**), not the '031 BSG variants. This is beside any point of interest here. Genencor also cites to a Borchert article comparing the Machius BLA crystal structure to the structure of a BA2 hybrid alpha-amylase. (BA2 was part BLA and part

BAN) **A8147-48**. This does not implicate the '031 patent. Likewise, Machius was discussed in an entirely different patent family than the '031 patent. **GPTO at 2** (citing **TE-665, A9064-65**). That family concerned a BAN-like enzyme that was described according to "exact atomic coordinates." **A9064**. Machius was offered to show differences between *Bacillus* and *Aspergillus* alpha-amylases (bacteria vs. a fungus). Novozymes' position was that a crystal structure for one alpha-amylase is hard to predict from other crystal structures, especially for inter-organism variants. **A9064-66**. Thus, Machius was cited to show uncertainty in the field. There is nothing pointing to the "surface loop," nor anything remotely material to BSG variants or the '031 patent.

Genencor urges that confidence in Machius has not been undermined, but this "confidence" game is insupportable. **GPTO at 2-5**. It ignores the presumed validity of the patent and Genencor's burden of proof. *Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006). Putatively locating Suzuki's deletion "in a surface loop" did not predict success for a 179,180 BSG variant. It had no effect on how a deletion experiment would be done or what outcome could be expected. **NPF ¶225, 362-63**. At most, Machius postulated from Suzuki's specific residues to a "promising field of experimentation" with only "general guidance as to the particular form," i.e. the loop. This speculation about "why" did not add to the "where and how" Suzuki already provided. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (general vs. specific teaching).[3]

Genencor says Machius told the protein engineer what to do, and so provided a reasonable expectation of success. **GPTO at 5-8**. A suggestion does not presume success; they are separate. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The "what do" already came from Suzuki, so Machius was cumulative. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1574-75 (Fed. Cir. 1997) ("reference teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO"). Machius gave no more help, and did not lead to the empirical superiority of the claimed variants. **NPTB at 6, 31-32; NPTO at 11.**

[3] Suzuki does not make the invention obvious either. **NPTB at 28; NPTO at 21**.

Machius states: "None of the above mentioned theories is able to explain satisfactorily the enhanced thermostability of BLA." **TE-173, A8384**. Genencor claims that this only applies to *other* theories, not the loop theory. **GPTO at 3**. The reference is explicit, and Dr. Machius cannot rewrite it from the witness stand to serve Genencor. *United States Filter Corp. v. Ionics, Inc.*, 68 F. Supp. 2d 48, 62 (D. Mass. 1999) (testimony by author does not illuminate what ordinary artisan would consider article to disclose); *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1364 (Fed. Cir. 2001). The loop is plainly one of the "above mentioned theories" (**A8384**) and is included in a need for "further structural information" (**A8385**). This theory "cannot be completely judged by our study" (**A8384**).[4] It suffers from "a lack of the three-dimensional structures of BAA [BAN] and of the [Suzuki] mutants described above." ***Id.*** Machius "could not detect special interactions" to explain increased thermostability, and was equivocal: "This loop is enlarged in BAA [BAN] by two extra residues, which could cause increased mobility" and a corresponding "decreased thermostability." ***Id.*** The defects in the Machius BLA structure, and the lack of atomic coordinates at the relevant time, are further reasons to doubt the ability of an ordinary skilled artisan to make trustworthy predictions. **NPF ¶226-30.** In 1995 the person of ordinary skill in the art would recognize these important qualifications. He or she would not confidently rely on the loop theory as a recipe or expectation of success. He would understand that many uncertain theories were around, and no reliable guidance was available. **A6523:10-17**.

Machius is said to offer Suzuki Region I as "a determinant of thermostability in BLA," *i.e.*, "making the deletion in BAN increases its thermostability by virtue of shortening the loop." **GPTO at 6** (emphasis in original). Even if true, which Machius questioned, this does not lead anywhere. Genencor's own conclusion makes this clear: "Thus, Machius '95 tells the protein engineer of ordinary skill what change to make -- the deletion at 179 and 180 -- and in what enzyme to make it

[4] Genencor notes that "completely" and "by our study" are not quoted in **NPTB at 7**, and suggests wrongdoing from its ignorance. The omission was inadvertent, and the full quote supports Novozymes. A theory that "cannot be completely judged by our study" is not a confident endorsement, especially when crucial data was admittedly lacking. **TE-173, A8384-85**.

-- BSG, in order to improve thermostability." ***Id.*** *This is unequivocally no more and no less than what already came from Suzuki and Bisgärd-Frantzen.* **NPTO at 11; NPF ¶400.** There was nothing more in Machius to empower success. *Regents,* 119 F.3d at 1575-76.

Further evidence that the loop was not a reliable "determinant" comes from Genencor's Dr. Zeikus, in a paper he co-authored (**TE-178**), and which Genencor and Dr. Machius relied on as "art that was available to protein engineers in 1995" (**A5693:3-24**). Dr. Machius noted that "shorter loops" (**A5694:2-18**; **TE-178 at 8511**) was one of many theories in the paper. **A8510-14**. The loop mechanism was tentative: "emerging data suggest their potential role in protein stabilization." **A8513**. "[L]oops might contribute significantly to thermozyme stability." **A8514**. Though maybe promising (**A8515**), uncertainty "prevents the definition of universal protein stabilization mechanisms. All of the proposed rules for amino acid substitutions between mezozymes and thermozymes … have been contradicted" (**A8510**).

Like making BAN more like BLA, these theories were for making a low-stability mezozyme more stable, by "replacing a mezozyme's residue with the one present in its thermophilic counterpart" (**A8514**). Improving a stable enzyme like BSG is different (**A8515**):

> Further stabilization of thermozymes represents an exciting challenge .... With enzymes approaching the upper limit of known protein thermostability, the extent to which they can be further stabilized is unknown.

Contrary to Genencor (**GPTO at 6**), the ability to improve BSG, and if so how much, was unpredictable, a loop theory notwithstanding. Dr. Arnold agreed about these theories: "By no means are they a recipe." **A6509:5; A6404:3-6505:17; A6509:1-6510:6**. "The only recipe for success is you go and make the protein. There are no recipes for success for protein engineering in these … references. There is a lot of confusion." **A6529:24-6530:2**.[5]

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[5] Genencor back-pedals on its witnesses. **GPTO at 6-7, n. 7,8**. Testimony is an ex-change and includes the question and answer. Machius and Zeikus agreed a double-deletion was worth trying but was unpredictable. **A5720:19-5722:4; A5739:24-5740:2; A6107:2-12.** Novozymes also never argues a need for "absolute predictability" or "exact magnitude" in the prior art. **GPTO at 7-8, 9**. Genencor's objections to this straw-man are irrelevant.

This is an invitation to experiment *without* a reasonable expectation of success. *In re Dow Chemical*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("obvious to experiment" not the standard for obviousness). Suzuki says that three alpha-amylases are homologous and 176,177 BAN variants had improved stability, close to BLA. **NPF ¶170-172**. Bisgärd-Frantzen said these alpha-amylases are highly homologous, and 176,177 of BAN aligns with 179,180 of BSG. **NPF ¶176-178**. Machius says that Suzuki's 176,177 BAN deletion is in a loop. **NPF ¶222-23.** Putting this together, Suzuki and Bisgärd-Frantzen hinted that deleting 179,180 in BSG was worth a try. Machius hinted that shortening the loop was worth a try. Deleting the Suzuki residues is what would shorten the Machius loop: these are basically two ways to say the same thing. There was nothing new to tell the artisan what to do, or how to do it, that would in any way improve his chance for success with BSG. **NPF ¶225.**

Genencor cannot rely on the '031 patent itself as proof of its obviousness. **GPTO at 7-8**. The patent is not prior art. Predictions made by inventors, who are not persons of ordinary skill, cannot be applied against the claims. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 874 (Fed. Cir. 1985). This is a classic effort to hijack the invention with hindsight from the patent. *Life Technologies, Inc. v. Clontech Laboratories, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). Further, working examples are not required. *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970); *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). An experiment was done later and was submitted to the PTO. **TE-508**. The results turned out to be phenomenal. **NPF ¶192, 354.** *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995). Genencor confuses whether the '031 patent teaches how to make and use BSG variants (enablement), with whether prior art for BAN variants predicted reasonable success for BSG (obviousness). These are different inquiries under different statues: 35 U.S.C. §103(a) and §112.[6]

[6] In *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005), the inventors "failed to demonstrate sufficient utility and therefore cannot establish enablement," for a cancer drug, and without dosages etc. *Id.* at 1322. Here, the '031 patent gives ample guidance on how to make and use thermostable BSG variants, whose utility has never been questioned.

B. The Patented BSG Variants Are Affirmatively Non-obvious

The unexpected results in the Borchert Declaration are strong. Despite Genencor's many criticisms, it has not rebutted these results with any experiments or credible evidence. **NPTB at 31; NPTO at 19.** The best Genencor can do is hand-waving by Dr. Klibanov. **GPTO at 8-9**. There is no basis for his subjective notion that only something more than an order of magnitude better could qualify as a surprising improvement. **A5817:23-5818:1; NPTO at 23**; *Motorola, Inc. v. Interdigital Technology Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997) (rejecting conclusory expert); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985). Also, a protein engineer would consider practical effect, which Klibanov ignored. **NPTO at 23.** The proof in the actual pudding was that the BSG variant is very much better in end-use applications than the ordinary artisan could reasonably have foreseen. **NPF ¶354**.

The improvement in Dr. Borchert's study was much more than an obvious incremental increase. **NPF ¶352-54;** *Chupp*, 816 F.2d at 646; *Soni*, 54 F.3d at 751. It was a large, unexpected and important difference, proving non-obviousness. ***Id.*** It was also a difference in kind. The new alpha-amylase can be used where others could not, including the closest prior art. The BSG variant works at high temperature and low calcium for days instead of hours (for BSG wild-type) or minutes (for BAN). *Id.*; **NPTO at 33; NPF ¶192.** This solved a hard problem for industry, is in great demand, has no easy alternatives, and provides exceptional economic benefits.[7]

Genencor would mix and match data, comparing selected results from one experiment to another without regard for purpose, test conditions, or good scientific practice. Thus, Klibanov is relied on to interpret Suzuki as showing a 25-fold improvement for "the 179,180 [*sic:* 176,177] deletion in BAN" (**GPTO at 8-9**). Suzuki had no BSG, and was comparing BAN to BLA with unusually high calcium. **NPF ¶174-75**. Dr. Borchert was comparing BSG to BAN, under the stated

[7] The patented variants are useful with low calcium, an important goal not addressed by the prior art. **TE-101, at 9:48-59, 9:62-66, 10:40-48, and 11:41-65; NPF ¶44.** Genencor insists on Suzuki's high calcium, which would eliminate evaluation of this benefit. The prior art did not predict that BSG thermostability be so high for so long, without help from calcium. **NPTO at 17.**

and important low-calcium conditions. **NPF ¶196-98.** Genencor cannot use the 25-fold number from Suzuki's different study as a cross-check for the Borchert study.

Genencor would sweep away objective considerations of non-obviousness by suggesting that Spezyme Ethyl might be a success because of price. **GPTO at 9-10**. Genencor overlooks that the nexus between commercial success and the patent is its own headstrong infringement. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988) (nexus is shown when "the thing...that is commercially successful is the invention disclosed and claimed in the patent"). Customers were demanding a high-performance product. Without Spezyme Ethyl and its use of the patented 179,180 BSG deletion, Genencor could not supply this demand. **NPF ¶233-35.** The invention was co-opted because it answered a pressing need and addressed a difficult problem that Genencor otherwise failed to solve.[8] But for its infringement, Genencor would not have been able to take *any* sales away from Novozymes and its Liquozyme SC product. Spezyme Ethyl is a commercial success because it has the needed properties, which are undoubtedly provided by the patented 179,180 BSG deletion. **A5040:9-14.** Genencor cannot avoid this by creating a price war or touting its customer service. *Demaco Corp.*, 851 F.2d at 1392; *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997).

Genencor's patent application flatly contradicts the positions it advances here. **[NPTB at 34; NPF ¶237-41, 372.** Genencor does not say otherwise, and weakly complains that such evidence "is not dispositive." **GPTO at 11**. It is compelling nonetheless. For example, Genencor cited Machius as reporting an alpha-amylase crystal structure (**TE-202, A8532.20, ¶[0095]**), yet the 179,180 BSG variants were claimed as patentable over that citation (***Id.* at A8532.44,** e.g. claim 1). Genencor did not notice, think about or believe in its "loop theory" back then, or thought it did not matter. This is powerful evidence of immateriality and non-obviousness. In context with all of the evidence, it rebuts Genencor's invalidity or unenforceability defenses. *Polaroid Corp. v. Eastman Kodak Co.*,

[8] Contrary to **GPTO at 11**, Dr. Crabb squirmed, but he testified that Genencor had no alpha-amylase for the high-performance fuel ethanol segment of the market, its other efforts failed when needed, and Spezyme Ethyl was the only option. **A5046:17-21; A5048:21-5049:8.**

641 F.Supp. 828, 848 (D. Mass. 1985), *aff'd*, 789 F.2d 1556 (Fed. Cir. 1986); *Mosinee Paper Corp. v. James River Corp.*, 22 U.S.P.Q.2d 1657, 1661 (E.D. Wis. 1992); **Exh. A**.

Finally, it bears repeating that Novozymes is not required to prove the non-obviousness of its patent. 35 U.S.C. §282. Genencor argues backwards when it says that the evidence: "is simply not sufficient to outweigh the strength of the prior art." ***Id.***, The burden is on Genencor to prove that the prior art outweighs the invention, by clear and convincing evidence. *Gillette Co. v S.C. Johnson & Son, Inc.*, 919 F.2d 720, 722-723 (Fed. Cir. 1990), *citing American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (burden is not lessened by prior art not before the PTO).

C. There Was No Misconduct Regarding Machius Or The Borchert Declaration

1. Machius Was Never Seen As Relevant And Was Innocently Omitted

Novozymes has consistently explained that Machius '95 is less relevant and cumulative to Suzuki and Bisgärd-Frantzen. **NPTB at 36-38; NPTO at 10-15**. It did not have to be cited. *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1567-77 (Fed. Cir. 1996); *Haliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1440 (Fed. Cir. 1991). Machius and its "loop" is not material: it does not point to invalidity or contradict any position taken by Novozymes. 37 C.F.R. 1.56; *Purdue Pharma, L.P. v. Endo Pharms., Inc.*, 438 F.3d 1123, 1128-29 (Fed. Cir. 2006). Nor was it inequitable to overlook Machius when its relevance (if any) was very low, and when there was no palpable intent to deceive the PTO. **NPF, ¶216-232, 249-56, 393-401**.

Dr. Borchert and Mr. Garbell did not think to cite Machius and then decide not to. **NPF, ¶249-56**. Machius did not come up. They did not notice or understand it to be even questionably pertinent. They reviewed it in another context, concerned with comparing crystal structures. **NPF, ¶252**. In the interference, they considered whether the Machius crystal could be used to predict the effect of residue changes near the calcium binding site of an alpha-amylase. ***Id.*** This did not implicate Suzuki's mutants, loops in BAN v. BLA, or extrapolations to BSG. It did not ring any bell for the '031 patent, nor should it have. Machius summarized Suzuki but they knew about Suzuki. **NPF, ¶56-59**. They also knew of Machius' limitations. **NPF, ¶399**.

Thus, Genencor urges that Novozymes should lose its patent because Genencor thought of a way to assert Machius for this lawsuit, which Novozymes "incredibly" missed. **GPTO at 12**. However, oversight is not inequitable, even if it was grossly negligent. *Ulead Sys., Inc. v. Lex Computer & Mgmt. Corp.*, 351 F.3d 1139, 1148 (Fed. Cir. 2003). Here, it was understandable, not inequitable or even negligent, to miss the alleged Machius connection. **NPF, ¶216-232, 249-56, 393-401;** *Nordberg, Inc. v. Telsmith, Inc.*, 82 F.3d 394, 397 (Fed. Cir. 1996). This is so even if the theory has merit, although it does not. **NPTB at 36-38; NPTO at 10-15**. Genencor's hindsight arguments about Machius cannot be imputed to Borchert and Garbell as inequitable conduct.

Genencor actually is in the same boat as Novozymes. It cited Machius in its patent application for the same BSG variants, but only as one reference among many others, for its report on an early BLA crystal structure. **TE-202, A8432.20, ¶[0095]**. It was not singled out as close prior art or recognized as very pertinent. It was not seen as any impediment to patentability. At the very least, Genencor did not appreciate then what it says is so significant now. *Thus, it is easy to see how Genencor's present theory about Machius, developed for litigation, was missed by Dr. Borchert and Mr. Garbell -- just as it was missed by Genencor's inventors and attorneys*. This is not a new post-trial story. **GTPO, at 13**. These are the explanations at trial, and in the record for why the light bulb never went off for Novozymes. They are reasonable and true.

The core of Genencor's untenable obviousness and misconduct story is that (**GPTO at 14**):

> the crystal structure described by Machius '95 provides the structural basis for the stabilization observed by Suzuki, and therefore, increased motivation and confidence in making the Suzuki deletion in BSG.

This non-sequitur begs the question. It is illogical to assume that *because* the loop and deletions were observed together, one must *cause* the other. A *possible* link is proposed, along with other ideas, but all of them are rejected for lack of good proof. **NPF, ¶229**. Machius did not provide a reliable "structural basis" for Suzuki's observations, and did not say it did. It said that you would at least need the structure of Suzuki's BAN variants to go forward. **TE-173, at A8384-85**.

It also does not follow that Genencor's putative structural basis "therefore" increased confidence or motivation in making the deletion in BSG. Genencor does not point to any quantum

of confidence or motivation, and there is none. The experts agree that Suzuki provided a motivation to try, by giving the "structural basis" for doing so. Suzuki said to delete certain residues, which is where a protein engineer works. The engineer wants to know what residues to alter, via the DNA for the alpha-amylase gene. **NPF, ¶18-19**. Placing these residues in a loop is extraneous knowledge. A suggestion to "look for the loop" was less helpful and already superseded. **NPF, ¶223-32**.

Dr. Borchert and Mr. Garbell never saw Machius as a "close case" under the PTO's "when in doubt" guidance in MPEP §2004. **GPTO at 14**. No doubt ever arose. **NPF, ¶393-401**. Moreover, an error in judgment under the "when in doubt" principle would not be inequitable. The governing rule is 37 C.F.R. 1.56, not the MPEP. There must be compelling evidence of an intent to conceal material information, i.e. that contradicts patentability or an applicant's arguments. *Purdue,* 438 F.3d at 1129; *Kingsdown Med. Consultants v. Hollister, Inc.,* 863 F.2d 867, 876 (Fed. Cir. 1988). Failure to act on a doubt is not culpable, and Genencor cannot prove even that. **NPF, ¶393-401**. Mistake, inadvertence, even gross negligence, is not misconduct. *Nordberg* ,82 F.3d at 397; *Kingsdown,* 863 F.2d at 876. Even if hindsight shows it would have been better to cite Machius, e.g. to avoid this dispute, that does not make it inequitable to miss doing so. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1001-03 (Fed. Cir. 2006) The record is clear that Novozymes made no decision and took no deliberate action to withhold the reference or usurp the Examiner.[9]

Genencor's reliance on *Labounty Mfg., Inc. v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066, 1076 (Fed. Cir. 1992) is misplaced. There, on grounds of "experimental use," the patentee did not disclose the prior on-sale status of its own product, which had a feature it had relied on to distinguish the prior art. The patentee admitted this was a close question, which should then have been asked of the PTO. Here, no "close question" came to mind for Dr. Borchert or Mr. Garbell. **NPF, ¶393-401**. Armed with cynicism, Genencor tries to make innocence into guilt.

[9] Genencor misreads Mr. Garbell's testimony. **GTPO, at 15**. He spoke hypothetically, and never said that Machius would stand in the way of the patent. **NPTO at 13**.

Genencor argues similarly from another logical fallacy: that Novozymes had self-interest, and so must be guilty of inequitable conduct. **GPTO at 15**. Like any patent applicant, Novozymes had "motive" to obtain solid patent protection, including protection against aggressive competition from the likes of Genencor. **NPF, ¶119**; *Kingsdown*, 863 F.2d at 874; *Newell Window Furnishings v. Kirsch, Inc.*, 15 Fed. Appx. 836 (Fed. Cir. July 2, 2001) (nonprecedential) (no inference of deception from presumed bad motive); **Exh. B**. This is a legitimate patenting activity. ***Id.*** Inequitable conduct is not triggered by or proportional to the perceived value of the patent. Misconduct must be shown to have actually occurred, from clear, convincing and unrebutted proof of what really happened. *Purdue,* 438 F.3d at 1128-29. It cannot turn on the idea that Novozymes must have pursued legitimate interests and ends, but used bad ways and means.[10]

The testimony shows that Novozymes took its patenting activities and obligations very seriously, and at all times acted in good faith. It was important to address the closest prior art. **NPF, ¶186**. It was important to consider the best strategy and move forward in the "best possible way" (**A8169**). It was important to design a thorough and meaningful experiment (**A8170-71**). A good or bad outcome would have to be disclosed to the PTO. **NPF, ¶259**. Machius was not intentionally withheld. **NPF, ¶249-56, 393-401**. There was no intent to deceive. ***Id.*** Good faith and candor was upheld throughout. ***Id.*** It simply is not true, in fact or in law, that Novozymes' good faith "cannot be accepted" because of "mounting commercial pressures." **GPTO at 15-16**.[11]

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[10] Genencor relies on *Quock Ting v. United States*, 140 U.S. 417, 420-21 (1891) to find inequitable conduct from what it calls the "inherent improbability" of Novozymes' explanations at trial. **GPTO at 12**. This 19th-century Supreme Court immigration case in no way applies here. *Quock* has been cited once by the Federal Circuit, to reject untenable expert testimony, not to convict a patentee of quasi-fraud under a clear and convincing standard of proof. *U.S. Philips Corp. v. Windmere Corp.*, 861 F.2d 695, 704 (Fed. Cir. 1988). The rule for inequitable conduct cases is that a plausible explanation must be credited. *Dayco Prods.*, 329 F.3d at 1367.

[11] Genencor faced worse commercial pressure. But for Spezyme Ethyl, it had no competing product and came too late with its own patent application. **TE-202, A8532.1; A5046:17-21; A5048:21-5049:8**. Genencor thus has a "motive" to overreach, as by alleging the bad faith of others. Its infringement "must" be in bad faith and its defenses are not trustworthy. In sum, there is no merit in the name-calling behind Genencor's "commercial motive" misconduct claim.

Novozymes explained what happened and its good faith must be accepted. Contrary proof of guilt cannot be extracted from Genencor's insinuations. *Dayco Prods.*, 329 F.3d at 1367; *FMC Corp. v. The Manitowoc Co.*, 835 F.2d 1411, 1417 (Fed. Cir. 1987) (no "inference on an inference" indictment); *Corning Inc. v. SRU Biosystems*, 418 F. Supp. 2d 596, 601 (D. Del. 2006) ("unsupported, rank speculation"). The totality of the circumstances, and a proper balancing of materiality and intent, all weigh in favor of presumed innocence. *Purdue,* 438 F.3d at 1128-29.

Also pertinent is *Warner-Lambert Co. v. Teva Pharms. USA*, 418 F.3d 1326, 1347 (Fed. Cir. 2005). There, even when faced with non-disclosure of a highly material reference (not so here), the inventors "acted with subjective good faith," because at the time, "they simply did not think it had any relevance to their application. In other words, they did not appreciate its materiality."

2. The Borchert Declaration Is Trustworthy

Genencor says: "Novozymes does not provide any convincing evidence which defends its manipulation of and misrepresentations about the underlying [Borchert] experiment" (**GPTO at 16**). This presumes the experiment was bogus and that Novozymes must respond with "convincing evidence." Genencor tries again to shift the burden and must fail. It was for Genencor to prove, by clear and convincing evidence, that the Borchert study was misrepresented. *Purdue,* 438 F.3d at 1128-29. Genencor has not done so, nor shown that anyone had a dishonest purpose. Exculpatory evidence from Novozymes should not even be needed, although it has been amply provided. **NPF, ¶257-65, 402-08**; *Tegal Corp. v. Tokyo Elecron Am.*, 257 F.3d 1331, 1349-50 (Fed. Cir. 2001).

First, the half-life of the BAN wild-type enzyme was not exaggerated by a lack of preheated buffer or ramp up time. Dr. Borchert used a rapid-heat PCR thermocycler with thin test tubes, which was standard at the time. It was a reasonable machine to use for rapid heating. **NPF, ¶200-06**. There is no evidence that this approach would make a difference or that Novozymes thought it would. There is no evidence of predicate knowledge or even a means to perpetrate the accused offense. There is no evidence that anyone meant to commit an offense or that the offense occurred.

NPF, ¶257-65, 402-08; *Hoffmann-La Roche, Inc., v. Promega Corp.*, 323 F.3d 1354, 1360-63 (Fed. Cir. 2003) (inventor's explanation, corroborated by expert, precluded inference of deception).[12]

Another serious problem is that Genencor cannot take data and results from one experiment and substitute it for data and results in another. **GPTO at 19**. It is wrong to use the BAN half-life from Suzuki as a comparator for Borchert, especially when Genencor argues that Suzuki's high calcium would influence the result. Genencor also cannot use the unheated (.435 min.) BAN half-life from the Tams ramp-up study as a replacement for Dr. Borchert's data. **GPTO at 19**. It is wrong for Genencor to selectively swap data from different studies, recalculate the results to suit its purpose, and then accuse Novozymes of inequities based on its own post-trial manipulations.

From the ramp-up study, Dr. Arnold found that the half-life of the BAN wild-type was 0.435 minutes with unheated buffer and 0.469 minutes with preheated buffer. **TE-208R, A8541**. The half-life for preheated buffer was longer than for unheated; the opposite of what Dr. Klibanov predicted. He assumed that the half-life in preheated buffer would be lower. **A6552:25-6553:22**. His theory was that less heat would deliberately allow BANwt to last longer, the BANdel increase would be understated, and the BSG comparison would be overstated. **A6544:15-21; A5799:2-6; A6553:1-25**. The ramp-up experiment showed that this is not so. **NPF, ¶204-05**. The difference between unheated and preheated samples (0.435 vs. 0.469) was not significant.[13] The thermocycler gave enough heat whether or not the buffer was preheated. **NPF, ¶200-06**. Preheating and ramp-up do not undermine the results or change the conclusions. ***Id.*** There is absolutely no hint of foul play.

There is no problem with calcium either. **NPTB at 38-39; NPTO at 17**. Genencor's patent application varies calcium according to purpose, using 5 mM in one example, 4 mM in another, and 20 ppm in a third. **A8532.25-26, ¶[0129, 0131, 0141]**. Also, "[t]he variant alpha-amylases [of

[12] Genencor's patent application corroborates that preheating was not required. It was not done even for short sample times like in Dr. Borchert's work. **A8532.25, at ¶[0129-133]**; **A6541: 4-11**. Characterizing Dr. Crabb as saying that "Genencor might preheat" (**GPTO at 17**) shows that it might not preheat. Anyway, he described a method that did not preheat. **NPTO at 24**.

[13] This is not 0.435 vs. 0.9 as Genencor tries to pass off here, by using data from different studies that are not interchangeable. *Moreover, Genencor never did any experiment the way it says should be done.* The only evidence is that it would not matter. **NPF, ¶185, 204-05**.

the] invention are contemplated to provide important advantages when compared to wild-type Bacillus alpha-amylases," for example "improved stability in the absence of calcium ion." **A8532.24, ¶[0123]**; **A8532.14, ¶[0009]; A8532.14, ¶[0011]**. A comparison for improved stability without calcium would be done with little or no calcium, just as Dr. Borchert did. It would not be done at high calcium like Suzuki. **NPF, ¶196-99**. And again, Genencor has no experiments to show what difference any of its arguments might make. **NPF, ¶185**.[14]

Genencor also makes a tempest in a test tube over alleged omitted data. There was nothing wrong here, as the record and briefs make clear. **NPF, ¶207-13; NPTB at 38-40; NPTO at 15-20**.

For the 2881 minute sample, Genencor argues that two wrongs should make a right. **GPTO at 20**. Evaporation of the sample was observed and the reading was lower than expected, not higher. **NPF, ¶210.** In other words, the sample was completely out of whack, but Genencor says it should be used anyway. Dr. Borchert obviously did the right thing; he discounted an unreliable sample.

Genencor has no quarrel with discounting the readings for 20/40 minute samples that precipitated, while using the twin 20/40 minute samples that did not. **GPTO at 20**. Genencor also is okay with discounting one 2940 minute reading (*Id.*), because it showed higher than 100% activity after more than 2 days (**A6547:14-16; A5645:8-13; TE-668 at A9097**). This reading also showed precipitate, adding to the confusion. *Id.* The other 2940 minute reading was questionable because it was much too low compared to its twin at ~120% (*Id.*). At ~53% (*Id.*) it was also unaccountably *lower* than the next reading of 61% at 4200 minutes (2.9 days). **TE-508, A8859**. These issues put the sample and both readings in question; they were properly excluded. **NPF, ¶211-12**. Even if this data point is used, the BSG variant is still within the 5-6 fold increase in the

[14] The '031 patent also shows that 0.1 mM is proper to compare enzymes at low calcium. **A6092:23-25; A7022 at 30:62-67; A6536:2-7**. Genencor argues that the assay disclosed in the patent is irrelevant, because the calcium has to be right for the "heating step." **GPTO at 18**. This is nonsensical. Just after citing 0.1 mM calcium, the '031 disclosure says, "The test is performed in a water bath at the temperature of interest." **A7022 at 30:62-67**. This is a thermal inactivation test. And different calcium levels at different steps are not disclosed anyway.

Declaration. ***Id.*** There was no material omission or misrepresentation. There is no evidence that Dr. Borchert made a calculated decision to fool the PTO. He made an honest expert judgment, period.

Complaints about the BSG variant half-life are based on pure speculation: "if" the variant does not obey first order kinetics, the Declaration "may have overestimated the relative improvement of BSG versus BAN" (**GPTO at 21**). This cannot be clear and convincing evidence of wrongdoing. *Hoffmann-La Roche*, 323 F.3d at 1360-63. Novozymes used well-accepted methods to calculate half-life from available data (**NPF, ¶214-25**), and disclosed its approach to the PTO. **NPF, ¶402-08**. The same methods are found in Genencor's patent application. **A6542:10-14**.

The only "evidence" of deceptive intent offered by Genencor is that Novozymes had a good reason to want the patent: it wanted to stop Genencor from using a BSG variant that Novozymes invented, disclosed in a patent application, and diligently sought to claim. **GPTO at 23**. This is evidence of competition; it is very far from a threshold deceptive intent that could prove misconduct. Genencor's provocation is not bad faith by Novozymes. There is no suspicious timing either. That Genencor came out with Spezyme Ethyl faster than Novozymes got the patent is not bad faith by Novozymes. *Kingsdown*, 863 F.2d at 874; *Newell*, 15 Fed.Appx. at 839 (**Exh. B**).[15]

Genencor cites *Merck & Co., Inc. v. Danbury Pharma, Inc.*, 873 F.2d 1418, 1420-22 (Fed. Cir. 1989), where contradictory statements were made, and a comparison of the drug to the closest prior art was given to the FDA but not to the PTO. Here, Novozymes has always seen Suzuki as the closest prior art. *See* n.2, above. It compared the invention to that prior art in a fair and duly reported experiment. Genencor's nitpicking over the experiment and its reliance on *Merck* only illustrates its failure to present any evidence to compel an inference of deceptive intent.

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[15] Genencor cites to *Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp.*, 424 F.3d 1347 (Fed. Cir. 2005). **GPTO at 25-26**. Here, the inventor and attorney legitimately saw nothing relevant or calling for inquiry. They both explained how Genencor's view of Machius and of the Declaration were understandably not thought of during the '031 prosecution. They acted reasonably and gave evidence of good faith. *See also* §II.C.1, above.

Genencor relies on numerous cases which mostly pre-date current Federal Circuit precedent. All of them are extreme and distinguishable.[16] They involved patentees who confessed to falsifying evidence, or who blatantly fudged or withheld entire experiments, or who conspicuously fabricated, omitted or mischaracterized key results. No case went against a patentee who diligently reported the conditions and results of an experiment, and omitted unreliable measurements. One case, *Cosden Oil & Chemical Co. v. American Hoechst Corp.*, 543 F. Supp. 522, 553 (D. Del. 1982), distinguished their facts here from its holding there:

> [T]his is not a situation in which an applicant has a substantial amount of test data, submits to the PTO data which are fairly representative of those tests, and fails to report several aberrational data points.

Dr. Borchert's "aberrational data points" were properly omitted. There is no taint of fraud.

Finally, Genencor relies on *Corning Glass Works v. Anchor Hocking Glass Corp.*, 253 F. Supp. 461 (D. Del. 1966), to say that inequitable conduct occurred from uncertainty. We don't know what might have happened if Machius was cited or Dr. Borchert gave more detail in his Declaration. **GPTO at 26**. Genencor's quote is not in *Corning*, although it is attributed to *Corning* by *CPC Int'l, Inc. v. Standard Brands, Inc.*, 385 F. Supp. 1057, 1068 (D. Del. 1974). Nevertheless, the idea that an entire patent family should stand or fall by this "avoidance of doubt" threshold is repugnant and has long been overruled. Oversight or mistake is not culpable even if it was grossly negligent; there must be a real intention to do the dirty deed, proven from a clear and convincing totality of the circumstances. *Nordberg,* 82 F.3d at 397; *Kingsdown,* 863 F.2d at 876. *See also*, *Hoffmann-La Roche*, 323 F.3d at 1362-63. That court affirmed inequitable conduct on one ground (past tense in a prophetic example), but reversed on non-disclosure of experimental results, because the patentee had a good scientific explanation. The dissent is also illuminating (*Id.* at 1373): "This case illustrates the ease of opportunistic challenge to the conduct of experimental science in [a] patent context." The patent and its science should not be "high stakes hindsight." This risk "has no countervailing public benefit ... the only beneficiary is the infringer who destroys the patent."

[16] These are the cases cited in **GPTO at 22, 24-26**.

3. There Is No Issue of "Prosecution Laches" In this Case

The laches claim is frivolous. **GPTO at 27**. Genencor frowns at claims that were narrowed in January 2004 and broadened in September 2004 (**TE-101, A633-37; A7733-38**). The Borchert experiment was done in the interim. ***Id.,* A7739-49**. Nine months cannot be an egregious case of prosecution laches. *Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP*, 422 F.3d 1378, 1385 (Fed. Cir. 2005) (18-39 years); *In re Bogese II*, 303 F.3d 1362 (Fed. Cir. 2002) (12 re-filings). Further, patent claims can be amended, and covering a competitor's product is a very good reason to do so. *Kingsdown*, 863 F.2d at 874; *State Indus., Inc. v. A.O. Smith Corp.*, 751 F.2d 1226 (Fed. Cir. 1985). Taking time to do experiments and confront the prior art is consistent with the duty of candor and is entirely proper. *Symbol*, 422 F.3d at 1385 (Fed. Cir. 2005). There is no basis for Genencor's prosecution laches defense. **NPF, ¶409-12**.

D. Genencor's Distorted Claim Terms Do Not Save It From Infringement

1. "Parent *Bacillus stearothermophilus* Alpha-amylase"

Genencor makes a startling claim that "parent *B. stearothermophilus* alpha-amylase" does not mean a real enzyme or anything "actually produced" by a BSG alpha-amylase gene. **GPTO at 29.**[17] These terms and the claims that use them are not about imaginary enzymes or reference sequences. **TE-100 at A7040**. Genencor points to exemplary parents in a "first aspect" of the invention (**GPTO at 30-31**), but examples are not a definition. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005). Also, Novozymes has relied on the '031 passages cited by Genencor. **NPF ¶80-81; NPTB at 8; NPTO at 32**. These embodiments coincide with and do not alter the plain meaning of the claim terms. They clearly do not narrow to "SEQ. ID NO. 3." **NPF, ¶80-84**.

The file history does not do this either. **GPTO at 32-33**. Genencor misconstrues exchanges with the PTO about whether "variant" should be narrowed by additional limitations such as "alpha-

[17] Genencor also says "wild-type" has been left out. **GPTO at 29**. The unaltered parent from which a variant is made is often a wild-type (**NPF, ¶86-89**), but is identifiable whether it is a wild-type or not, and can be compared as claimed. **A7040**. Plus, "wild-type" is not fatal. When Spezyme Ethyl is matched to its wild-type G997 parent BSG alpha-amylase, it infringes claims 1 and 5. It has only the 179,180 deletion and is >95% homologous to G997. **NPF, ¶136**.

amylase activity" or "percent homology" (and by how much). **TE-100, A7719-26**. None of this changed the ordinary meaning of any term into a special one. **NPTB at 13-22; NPTO at 27-40**.

There is no problem with definiteness either: the claims are simple. The variant is compared to the parent or BSG alpha-amylase it came from. Both are knowable and known. Fermentation conditions and allegedly different results do alter what the claim terms mean to a person of ordinary skill, nor cloud any one-to-one comparisons between parent and variant. **NPF, ¶135**. The G997 sequence is not a mystery, it is the one consistently found in Genencor's samples and documents. Genencor's hollow argument that G997 is not a parent or BSG alpha-amylase because it is truncated or made by fermentation is unfounded. **NPTO at 33-36**. There is also no confusion between G997, GZYME-G997 and ATTC 39,709; nor between strains, genes and enzymes. **GPTO at 36**. The BSG strain is ATCC 39,709. It carries a gene that produces the G997 alpha-amylase; the same gene and alpha-amylase used in the GZYME-G997 product. There is one G997 gene, one G997 alpha-amylase, and one sequence, just like Spezyme Ethyl. **NPF, ¶129-49; NPTO at 33-35**.

Genencor shifts gears to say its "514-515 amino acid" BSG alpha-amylase is an "actually expressed" protein; but immediately concedes that this is only what "a protein engineer expected" with "no evidence" of C-terminal truncation. **GPTO at 35**. Maybe these enzymes were expressed, but they were not fully sequenced. **NPF, ¶139-149**. Their length was estimated from DNA and molecular weight gels.[18] Truncation was not looked for. **A5181:18-20; NPTO at 33 n.13.** This is irrelevant anyway, because extrinsic time-dependent beliefs cannot be read into claim terms. **NPTO at 31-33**. Genencor also labors from stereotyping. It reasons from an observation about members of a class (alpha-amylases with 514-515 residues), to a conclusion about the entire class (all alpha-amylases have 514-515 residues). We know this is not true. Moreover, a characteristic, even if typical of a class, is not a definition of the class, nor of a claim term in a patent. ***Id***.

[18] *See* **TE-142, A8359-64; TE-568, A8940-43; TE-628, A8993-9002; TE-629, A9003-12; TE-630, A9013-24; TE-633, A9025-30; TE-634, A9031-36; TE-635 at A9037-44**.

2. "Percent Homology"

Novozymes does not construe percent homology as requiring GAP (GCG). **GPTO at 37.** Another program can be used, if it calculates percent homology in the same standard "exact match" way. **NPF, ¶97.** Genencor is also wrong to rely on Dr. Alber's extrinsic restatement ("how similar one entire sequence is to another"). **GPTO at 37.** Percent homology in the patent means percent identity (**TE-100, at A7009, 4:36-49**), determined in a conventional way -- exact matches are counted, not gaps. **NPF, ¶97.** This is exemplified by GAP (GCG). Other programs that work the same way can be used. **NPF, ¶99.**[19] Genencor ignores the intrinsic evidence in favor of extrinsic rhetoric, and misstates Novozymes' position in order to refute it. Worse, Genencor advocates that the only definition and exemplary implementation in the patent can never be used. It urges that some other definition and implementation must always be used. This cannot lead to the right claim construction. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1355 (Fed. Cir. 1998). Likewise, the alleged "need to know" about all sequence changes is a boondoggle. **GPTO at 39.** The protein engineer can of course answer other questions if they interest him. This is irrelevant to the one-to-one comparison disclosed and claimed in the patent. *Phillips*, 415 F.3d at 1319.

III. CONCLUSION

Genencor offers no defense for its infringement, except to press for its claim construction. **GPTO at 28.** That construction is wrong, and properly construed claims are infringed. Genencor also failed to carry its heavy burden on invalidity and unenforceability. Genencor inappropriately requests attorneys fees. This issue does not appear in the Pre-Trial Order (**A1008-1009 at §IV**). It has not been litigated and it has not been briefed. Furthermore, this is not a "special case" for such sanctions. *Argus Chemical Corp. v. Fibre Glass-Evercoat Co.*, 812 F.2d 1381, 1386 (Fed. Cir. 1987). Judgment in this case should be for Novozymes.

[19] There is no fatal contradiction in Dr. Arnold's testimony. *See* **NPTO at 37-38.**

Respectfully submitted,
YOUNG CONAWAY STARGATT & TAYLOR, LLP

Dated: May 12, 2006

Josy W. Ingersoll (No. 1088)
Rolin P. Bissell (No. 4478)
Andrew A. Lundgren (No. 4429)
1000 West Street, 17th Floor
Wilmington, Delaware 19801
(302) 571-6600
alundgren@ycst.com

Attorneys for Plaintiff Novozymes A/S

OF COUNSEL:
Joseph R. Robinson (*Pro Hac Vice*)
Robert C. Sullivan, Jr. (*Pro Hac Vice*)
Samuel S. Woodley (*Pro Hac Vice*)
DARBY & DARBY PC
805 Third Avenue
New York, New York 10022-7513
(212) 527-7700

CERTIFICATE OF SERVICE

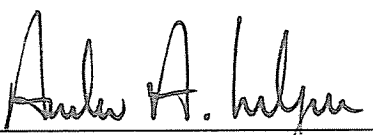
I, Andrew A. Lundgren, hereby certify that on the 12th day of May, 2006, I caused a copy of the foregoing document entitled "PLAINTIFF NOVOZYMES' POST-TRIAL REPLY BRIEF" to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

Donald E. Reid, Esquire
Jason Cincilla, Esquire
MORRIS NICHOLAS ARSHT & TUNNELL
1201 N. Market Street
P.O. Box 1347
Wilmington, Delaware 19899-1347

I further certify that on May 12, 2006, I caused a copy of the foregoing document entitled "PLAINTIFF NOVOZYMES' POST-TRIAL REPLY BRIEF" to be served by hand delivery on the above-listed counsel of record and on the following non-registered participants in the manner indicated:

BY FEDERAL EXPRESS

Kenneth R. Adamo, Esq.
Tharan Gregory Lanier, Esq.
JONES DAY
2822 Sand Hill Road, Suite 240
Menlo Park, CA 94025



Andrew A. Lundgren (No. 4429)
The Brandywine Building
1000 West Street, 17th floor
Wilmington, DE 19801
(302) 571-6600
alundgren@ycst.com

Attorneys for Novozymes A/S